IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BOARD OF APPEALS

In re application: **Group Art Unit: 1649**

Carter et al. **Examiner: S. Gucker**

Serial No. 10/010,245

Filed: December 7, 2001

For: A METHOD FOR MAKING HETEROMULTIMERIC POLYPEPTIDES

APPELLANT'S APPEAL BRIEF

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CASES

Patent Docket No. P0927C2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Carter *et al.* Serial No.: 10/010,245 Filed: December 7, 2001 For: *A Method for Making Heteromultimeric Polypeptides*	Group Art Unit: 1649 Examiner: Stephen Gucker Confirmation No.: 8478
	Electronically Filed November 13, 2007

APPEAL BRIEF

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This appeal brief, filed on November 13, 2007 with a petition and fee for a Five-month extension of time, is responsive to the Final Office Action of Claims 25, 28, 39, 42-55, 57-81 mailed on February 12, 2007 ("Final Action"). A Notice of Appeal was timely filed herein on April 16, 2007 with the appropriate fee pursuant to 37 C.F.R. § 1.17(b).

Appellants hereby appeal to the Board of Patent Appeals and Interferences from the Final Action in this case.

The Commissioner is authorized to charge any additional fees, which may be required, including extension fees, or credit any overpayment to Deposit Account No. 07-0630.

I. REAL PARTY IN INTEREST

Genentech, Inc., of South San Francisco is the owner by assignment of the above-identified patent application. This application is a continuation of 08/974,183, filed November 19, 1997, now abandoned, which is a continuation of 08/399,106, filed March 1, 1995 (now U.S.P. 5,731,168). The assignment for the initial parent, U.S. Serial Number 08/399,106 was recorded on: May 8, 1995 at Reel 7516 and Frame 0500.

II. RELATED APPEALS AND INTERFERENCES

Appellant has no knowledge of any other appeals or interferences that will directly affect, be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

The present application was filed on December 7, 2001 with claims 1-38. In a telephone conversation of October 6, 2004, Claims 24-28 were provisionally elected for prosecution, pending rejoinder with Claims 1-23 and 29-38. In an amendment filed April 5, 2005, Claims 26-27 were cancelled, Claims 1, 25, 28 and 35 were amended and Claims 39-81 were added. In an amendment filed January 20, 2006, Claims 39-41 and 62 were amended and Claims 24 and 56 cancelled. For purposes of this appeal, Claims 1-23 and 29-38 are withdrawn, while Claims 25, 28, 39, 42-55, 57-81 are rejected and appealed herein.

IV. STATUS OF AMENDMENTS

No amendment was filed subsequent to the Final Office Action mailed February 12, 2007.

V. SUMMARY OF THE INVENTION

Summarized in the most basic form, the appealed claims relate to heteromultimeric polypeptides comprising a first and second polypeptide which meet at an engineered interface, wherein the engineered interface increases the ratio of heteromultimer:homomultimer formation than would be formed in the absence of the engineered interface.

More specifically, independent Claim 25 relates to an isolated heteromultimer comprising a first and second polypeptide which meet at an engineered interface, wherein said interface further comprises an interface of the first polypeptide and an interface of the second polypeptide. The interface of the first polypeptide comprises (i) a protuberance that is positionable in a cavity in the interface of the second polypeptide, (ii) a cavity into that is positionable in a protuberance of the second polypeptide, or (iii) both (i) and (ii). As a result of the engineered interface, the ratio of heteromultimer:homomultimer is greater than would be the case for a similar multimer having a non-engineered interface.

Support for heteromultimers comprising a first and second polypeptide that meet at an interface in which the first polypeptide comprises a protuberance which is positionable in a cavity in the interface of the second polypeptide, wherein either or both the protuberance or cavity have been introduced appears at least on page 9, lines 20-25.

Support for an "engineered" interface between the first and second polypeptides appears at page 8, lines 24-25.

Support for "heteromultimer" appears on page 12, line 22 to page 13, line 5.

Support for "first polypeptide" appears on page 14, lines 10-26.

Support for "second polypeptide" appears on page 15, lines 1-16.

Support for increasing the ratio of heteromultimer:homomultimer formation over multimers having non-engineered interfaces appears at page 10, lines 18-19.

Support for Claim 28, essentially directed to compositions of the heteromultimers of the invention in combination with pharmaceutically-acceptable carriers appears on page 9, lines 25-26.

Support for Claim 39, essentially directed to heteromultimers in which the first polypeptide comprises both protuberances and cavities which are positionable in cavities and protuberances, respectively, in the second polypeptide appears on page 12, lines 10-17, page 63, lines 6-18, Table 4, lines 18-20 (Page 61, lines 10-20), Figure 4 ("Double mutants") and Figure 7.

Support for Claims 42-43, essentially directed to an engineered protuberance or cavities, respectively, appears at page 23, lines 4-20.

Support for Claim 44 and 50, essentially directed to non-naturally occurring protuberances and cavities, respectively, appears on page 23, lines 17-20.

Support for Claim 45 and 51, essentially directed to naturally occurring protuberances, appears on page 23, lines 5-7.

Support for Claims 46-49, essentially directed to specific amino acid residues comprising protuberances, appears on page 21, lines 8-10.

Support for Claims 52-55, essentially directed to specific amino acid residues comprising cavities, appears on page 21, lines 23-25.

Support for Claim 57-60, essentially directed to interfaces that are in order of increasing specificity, immunoglobulin constant domains, CH3 domains, IgG domains and IgG1 domains, respectively, appears on page 19, lines 6-11.

Support for Claims 61-65, essentially directed to interfaces that are of the IgG2, IgG2A, IgG2B, IgG3 and IgG4 subtypes, respectively, appears at least in Figures 6A-6B.

Support for Claim 66, essentially directed to interfaces further comprising a binding domain appears on page 14, lines 11-5, page 15, lines 2-5 and page 15, lines 17-20.

Support for Claim 67, essentially directed to interfaces wherein the binding domain is an antigen binding domain appears on page 15, lines 17-20.

Support for Claim 68, essentially directed to interfaces wherein the binding domain is a ligand binding domain appears on page 15, lines 17-20 and page 18, lines 1-9.

Support for Claim 69, essentially directed to interfaces wherein the binding domain is a receptor binding domain appears on page 15, lines 17-20 and page 18, lines 10-14.

Support for Claim 70, essentially directed to interfaces wherein the binding domain is an enzymatic domain appears on page 15, lines 17-20.

Support for Claim 71, essentially directed to interfaces wherein the binding domain is an antibody variable domain appears on page 15, lines 17-20.

Support for Claims 72-74, essentially directed to heteromultimers that are multispecific antibodies, including bispecific and trispecific antibodies, respectively, appear on page 16, line 18 to page 17, line 18.

Support for Claims 75-77, essentially directed to heteromultimers that are immunoadhesin, including multi-specific and bi-specific immunoadhesins, appear on page 18, lines 15-24.

Support for Claims 78-70, essentially directed to heteromultimers that are heterodimers, heterotrimers or heterotetramers, respectively, appear on page 12, line 22 to page 13, line 5.

Support for Claim 81, essentially directed to an antibody-immunoadhesin, appears on page 18, line 25 to page 19, line 2.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

There is a single issue presented to the Board by the Final Office Action dated February 12, 2007.

Claims 25, 28, 39, 42-55 and 57-81 stand rejected under 35 U.S.C. § 112, First Paragraph, as allegedly failing to comply with the written description requirement for containing subject matter that is not described in the specification in such a way as to reasonably convey to one skilled that Applicants had possession of the claimed invention.

VII. ARGUMENTS

Claims 25, 28, 39, 42-55 and 57-81 stand rejected under 35 U.S.C. § 112, First Paragraph as allegedly failing to satisfy the written description requirement. The sole basis for the Examiner's rejection is that specification does not teach, in the context of the claimed heteromultimers, first polypeptides or second polypeptides that comprise both protuberances and cavities that occur simultaneously or concurrently.

Applicants strongly disagree, and respectfully traverse the rejection.

A. The Legal Standard for Written Description

The written description requirement prescribes that the specification must convey with reasonable clarity to those skilled in the art, that Applicants were in possession of the invention as of the filing date. *Moba, B.V. v. Diamond Automation, Inc.*, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003);) *Vas-Cath v. Mahurkar*, 19 U.S.P.Q.2d. 1111, 1116 (Fed. Cir. 1991). The burden of showing that the claimed invention is not described in the specification rests on the PTO in the first instance, and it is up to the PTO to give reasons why a description not in *ipsis verbis* is insufficient. *In re Wertheim*, 191 U.S.P.Q. 90, 98 (C.C.P.A. 1976). The determination is *factual* and depends on the nature of the invention and amount of knowledge imparted to those skilled in the art by the disclosure. *Vas-Cath* at 1116 (emphasis in original).

According to the M.P.E.P. §2163, an Applicant can show possession of the claimed invention by describing the claimed invention . . . using such descriptive means as words,

structures, figures, diagrams and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.* 41 U.S.P.Q.2d 1961, 1966 (Fed. Cir. 1997).)

B. The Disclosure Supporting Written Description

The disclosure of the current specification that is directed most particularly to the current dispute is presented schematically in Figure 4. In particular, the second "double mutant" shows a combination of a protuberance and a cavity in both the first and second polypeptides.

Applicants further provided specific examples of such double mutants in the Examples, Table 4, Figures 7 and 10. In particular, Table 4, lines 18-20 on page 61 describes double mutants of anti-CD3 (first polypeptide) of (1) T366Y:F405A, (2) T366W:F405W and (3) F405W:Y407A. These are matched with mutants of anti-CD4 (second polypeptide) of (1) T394W:Y407T, (2) T394S:Y407A and (3) T366W:T394S.

As defined in the specification on page 19, lines 17-21, a "protuberance" can be introduced by replacing at least a one amino acid residue with a replacement residue having a larger side chain volume. As further defined on page 21, lines 8-12, suitable replacement residues can be arginine (R), phenylalanine (F), tyrosine (Y) and tryptophan (W).

In a similar manner, a "cavity" (page 21, lines 17-22) may be introduced by replacing at least one amino acid residues with a replacement residue having a smaller side chain volume. As further defined on page 21, lines 23-25, suitable replacement residues can be alanine (A), serine (S), threonine (T) and valine (V).

Thus, with respect to the 3 double mutants described in Table 4, the following is described. For the first polypeptide (*e.g.*, anti-CD3), first mutant, the T366Y introduces a protuberance, while the F405A introduces a cavity. In the second mutant, both the T366W and F405W introduce protuberances, while in the third mutant, the F405W introduces a protuberance while the Y407A introduces a cavity. For the second polypeptide (*e.g.*, anti-CD4), the first mutant T394W introduces a protuberance, while the Y407T introduces a cavity. In the second mutant, both the T394S and Y407A introduce cavities, while in the third mutant, the T366W introduces a protuberance, and the T394S introduces a cavity. This provides explicit, experimental support for first and second polypeptides that comprise both a protuberance and a cavity.

Contrary to Applicants position, the Examiner alleges that the specification does not provide for a written description of multimers comprising a first and second polypeptide that comprise both protuberences and cavities. Applicants respectfully submit, that upon further reflection of the disclosure discussed above, and application of the appropriate legal standards, the present application does in fact, show possession of the claimed invention.

VIII. CONCLUSIONS

For the reasons given above, Applicants respectfully submit the present specification clearly describes, details and provides a written description for the claimed invention. As such, Applicants respectfully request reconsideration and reversal of the outstanding rejection of Claims 25, 28, 39, 42-55 and 57-81.

Respectfully submitted,
GENENTECH, INC.

Date: November 13, 2007

By: _____
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IX. CLAIM APPENDIX

25 (Previously presented). An isolated heteromultimer comprising a first polypeptide and a second polypeptide which meet at an engineered interface, wherein said engineered interface further comprises an interface of the first polypeptide and an interface of the second polypeptide:

(a) the interface of the first polypeptide comprises a protuberance that is positionable in a cavity in the interface of the second polypeptide, or

(b) the interface of the first polypeptide comprises a cavity that is positionable in a protuberance of the second polypeptide,

wherein the protuberance or cavity, or both, have been introduced into the engineered_interface such that a greater ratio of heteromultimer:homomultimer forms than for a multimer having a non-engineered interface.

28 (Previously presented). A composition comprising the heteromultimer of any of claims 25, 39, 57-59, 66, 75, and 81 and a pharmaceutically acceptable carrier.

39 (Previously presented). The heteromultimer of Claim 25 wherein the interface comprises both (a) and (b).

42 (Previously presented). The heteromultimer of Claim 25 wherein the protuberance has been introduced into the engineered interface.

43 (Previously presented). The heteromultimer of Claim 25 wherein the cavity has been introduced into the engineered interface.

44 (Previously presented). The heteromultimer of Claim 42, wherein protuberance comprises a non-naturally occurring amino acid residue.

45 (Previously presented). The heteromultimer of Claim 42, wherein the protuberance comprises a naturally occurring amino acid residue.

46 (Previously presented). The heteromultimer of Claim 45, wherein the protuberance comprises an arginine (R) residue.

47 (Previously presented). The heteromultimer of Claim 45, wherein the protuberance comprises a phenylalanine (F) residue.

48 (Previously presented). The heteromultimer of Claim 45, wherein the protuberance comprises a tyrosine (Y) residue.

49 (Previously presented). The heteromultimer of Claim 45, wherein the protuberance comprises a tryptophan (W) residue.

50 (Previously presented). The heteromultimer of Claim 42, wherein the cavity comprises a non-naturally occurring amino acid residue.

51 (Previously presented). The heteromultimer of Claim 42, wherein the cavity comprises a naturally occurring amino acid residue.

52 (Previously presented). The heteromultimer of Claim 51, wherein the cavity comprises an alanine (A) residue.

53 (Previously presented). The heteromultimer of Claim 51, wherein the cavity comprises a serine (S) residue.

54 (Previously presented). The heteromultimer of Claim 51, wherein the cavity comprises a threonine (T) residue.

55 (Previously presented). The heteromultimer of Claim 51, wherein the cavity comprises a valine (V) residue.

57 (Previously presented). The heteromultimer of Claim 25, wherein the engineered interface comprises an immunoglobulin constant domain.

58 (Previously presented). The heteromultimer of Claim 57, wherein the immunoglobulin constant domain is a C_H3 domain.

59 (Previously presented). The heteromultimer of Claim 58, wherein the C_H3 domain is from an IgG.

60 (Previously presented). The heteromultimer of Claim 59, wherein the IgG is of the IgG1 subtype.

61 (Previously presented). The heteromultimer of Claim 59, wherein the IgG is of the IgG2 subtype.

62 (Previously presented). The heteromultimer of Claim 59, wherein the IgG is of the IgG2A subtype.

63 (Previously presented). The heteromultimer of Claim 59, wherein the IgG is of the IgG2B subtype.

64 (Previously presented). The heteromultimer of Claim 59, wherein the IgG is of the IgG3 subtype.

65 (Previously presented). The heteromultimer of Claim 59, wherein the IgG is of the IgG4 subtype.

66 (Previously presented). The heteromultimer of Claim 25, wherein the first or second polypeptide further comprises a binding domain.

67 (Previously presented). The heteromultimer of Claim 66, wherein the binding domain is an antigen binding domain.

68 (Previously presented). The heteromultimer of Claim 66, wherein the binding domain is a ligand binding domain.

69 (Previously presented). The heteromultimer of Claim 66, wherein the binding domain is a receptor binding domain.

70 (Previously presented). The heteromultimer of Claim 66, wherein the binding domain is an enzymatic domain.

71 (Previously presented). The heteromultimer of Claim 66, wherein the binding domain is an antibody variable domain.

72 (Previously presented). The heteromultimer of Claim 25 which is a multi-specific antibody.

73 (Previously presented). The heteromultimer of Claim 72 which is a bi-specific antibody.

74 (Previously presented). The heteromultimer of Claim 72 which is a tri-specific antibody.

75 (Previously presented). The heteromultimer of Claim 25 which is an immunoadhesin.

76 (Previously presented). The heteromultimer of Claim 75 which is a multi-specific immunoadhesin.

77 (Previously presented). The heteromultimer of Claim 76 which is a bi-specific immunoadhesin.

78 (Previously presented). The heteromultimer of Claim 76 which is a heterodimer.

79 (Previously presented). The heteromultimer of Claim 76 which is a heterotrimer.

80 (Previously presented). The heteromultimer of Claim 76 which is a heterotetramer.

81 (Previously presented). The heteromultimer of Claim 25 which is an antibody-immunoadhesin chimera.